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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/625,708	07/24/2003	Donald J. Kyle	6750-174-999	8122

20583 7590 11/20/2006

JONES DAY
222 EAST 41ST ST
NEW YORK, NY 10017

EXAMINER

HABTE, KAHSAY

ART UNIT	PAPER NUMBER
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1624

DATE MAILED: 11/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/625,708

Applicant(s)

KYLE ET AL.

Examiner

Kahsay Habte

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 October 2006.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-96,99-108 and 111-207 is/are pending in the application.
- 4a) Of the above claim(s) 64-84,90-96 and 102-108 is/are withdrawn from consideration.
- 5) ☒ Claim(s) 21-41,62,86,88,89,99-101,111 and 144-199 is/are allowed.
- 6) ☒ Claim(s) 1,18,19,42,43,45,59,61 and 63 is/are rejected.
- 7) ☒ Claim(s) 2-17,20,44,46-58,60,63,85,87,112-143 and 200-207 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>10/26/2006</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Claims 1-96, 99-108 and 111-207 are pending in this application.

Response to Amendment

2. Applicant's amendment filed 10/26/2006 in response to the previous Office Action (04/27/2006) is acknowledged. Rejection of claims 1, 18-19 and 61 under 35 U.S.C. 103(a) has been maintained. The examiner has reinstated the obviousness rejection of claims 42-43, 45, 59 and 63 that were previously rejected (see Office Action 10/17/2005, item 4) over Toldy et al. *Acta Chimica Academiae Scieniarum Hungaricae* (1971), 69(2), 221-7.

This Office Action was not made final, because the examiner is waiting a response from the Chemical Abstract Services in regard to the source for these two "prior art compounds" 4-(6-chloro-3-pyridazinyl)-N-(4-ethoxyphenyl)-1-Piperazinecarbothioamide and 4-(6-methoxy-3-pyridazinyl)-N-(4-ethoxyphenyl)-1-Piperazinecarbothioamide.

3. The examiner requested the Chemical Abstract Search (CAS) in Columbus, Ohio to clarify the source of these two prior art compounds. The two prior art compounds that showed up in Toldy et al. that were used for the obviousness rejection are assumed to be part of Table I in Toldy et al. To this day, the examiner did not get a definitive answer from CAS. The CAS help desk is reluctant to indicate that these two compounds are indexed improperly. They take a position that "the scientist at that time indexed these two compounds for good reasons".

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 18-19 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Toldy et al. *Acta Chimica Academiae Scieniarum Hungaricae* (1971), 69(2), 101-122 (English translation attached). Cited reference in English teaches a compound of interest: 4-(6-chloropyridazinyl-3-yl)-N,N-diethylpiperazine-1-carboxamide that has therapeutic benefit for the treatment of TB. Said compound is almost the same as applicants when applicant's formula (III) has the following substituents:

$R^1 = \text{Cl}$; $n = m = 0$; $A = \text{NH}$; and $R^4 = \text{ethyl}$.

The only difference between the prior art compounds and applicants' compounds is that the position of the chloro substituent on the pyridazinyl ring and the substitution on amino group (i.e. $A = \text{NH}$ vs $A = \text{N-C}_2\text{H}_5$). The prior art compounds have the chloro and substituent at the 4-position of the pyridazinyl ring, but applicants require that the substituents of R^1 to be fixed at the 6-position of the pyridazinyl ring (i.e. $R^1 = \text{Cl}$ is fixed at 6-position). Thus, the only difference between applicants' compounds and the prior art compounds is the position of the chloro substituents on the pyridazinyl ring. It is well established that position isomers are prima facie structurally obvious even in the

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absence of a teaching to modify. The isomer is expected to be preparable by the same method and to have generally the same properties. This expectation is then deemed the motivation for preparing the position isomers. This circumstance has arisen many times. See: *Ex parte Englehardt*, 208 USPQ 343, 349; *In re Mehta*, 146 USPQ 284, 287; *In re Surrey*, 138 USPQ 67; *Ex Parte Ulliyot*, 103 USPQ 185; *In re Norris*, 84 USPQ 459; *Ex Parte Naito*, 168 USPQ 437, 439; *Ex parte Allais*, 152 USPQ 66; *In re Wilder*, 166 USPQ 545, 548; *Ex parte Henkel*, 130 USPQ 474; *Ex parte Biel*, 124 USPQ 109; *In re Petrzilka*, 165 USPQ 327; *In re Crownse*, 150 USPQ 554; *In re Fouche*, 169 USPQ 431; *Ex parte Ruddy*, 121 USPQ 427; *In re Wiechert*, 152 USPQ 249, *In re Shetty*, 195 USPQ 753.

For example, "Position isomerism has been used as a tool to obtain new and useful drugs" (*Englehardt*) and "Position isomerism is a fact of close structural similarity" (*Mehta*, emphasis in the original). See also MPEP 2144.09, second paragraph.

The second difference between applicants and the prior art compound is in the definition of variable A. Applicants' compounds have -NH-, but the prior art compound has -N-C₂H₅. Compounds that differ only by the presence or absence of an extra methyl group or two are homologues. Homologues are of such close structural similarity that the disclosure of a compound renders *prima facie* obvious its homologue. The homologue is expected to be preparable by the same method and to have generally the same properties. This expectation is then deemed the motivation for preparing homologues. Of course, these presumptions are rebuttable by the showing of

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unexpected effects, but initially, the homologues are obvious even in the absence of a specific teaching to add or remove methyl groups. See *In re Wood*, 199 USPQ 137; *In re Hoke*, 195 USPQ 148; *In re Lohr*, 137 USPQ 548; *In re Magerlein*, 202 USPQ 473; *In re Wiechert*, 152 USPQ 249; *Ex parte Henkel*, 130 USPQ 474; *In re Fauque*, 121 USPQ 425; *In re Druey*, 138 USPQ 39. In all of these cases, the close structural similarity between two compounds differing by one or two methyl groups was itself sufficient show obviousness.

Response to arguments

Applicant's argument filed 10/26/2006 has been fully considered but it is not persuasive.

Applicant's argument is well taken, but it is not persuasive enough to overcome the obviousness rejection. Applicant's argument was based on Toldy IIE (Toldy et al. *Acta Chimica Academiae Scieniarum Hungaricae* (1971), 69(2), 221-7 and not on the translated document Toldy et al. *Acta Chimica Academiae Scieniarum Hungaricae* (1971), 69(2), 101-122. The compound of interest: 4-(6-chloropyridazinyl-3-yl)-N,N-diethylpiperazine-1-carboxamide is disclosed at page 5 (Table 1, compound V).

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

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invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 42-43, 45, 59 and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Toldy et al. *Acta Chimica Academiae Scientiarum Hungaricae* (1971), 69(2), 221-7. Cited reference in German language teaches two compounds of interest: 4-(6-chloro-3-pyridazinyl)-N-(4-ethoxyphenyl)-1-Piperazinecarbothioamide and 4-(6-methoxy-3-pyridazinyl)-N-(4-ethoxyphenyl)-1-Piperazinecarbothioamide that have therapeutic benefit for the treatment of TB (see English abstract of said article) . Said compounds are almost the same as applicants when applicant's formula (III) has the following substituents:

$R^1 = \text{Cl or OCH}_3$; $n = m = 0$; $A = \text{NH}$; and $R^4 = \text{phenyl substituted with ethoxy at 4-position}$.

The only difference between the prior art compounds and applicants' compounds is that the position of the chloro and methoxy substituents on the pyridazinyl ring. The prior art compounds have the chloro and the methoxy substituents at the 4-position of the pyridazinyl ring, but applicants require that the substituents of R^1 to be fixed at the 6-position of the pyridazinyl ring (i.e. $R^1 = \text{Cl or OCH}_3$ are fixed at 6-position). Thus, the only difference between applicants' compounds and the prior art compounds is the position of the chloro and methoxy substituents on the pyridazinyl ring. It is well established that position isomers are prima facie structurally obvious even in the absence of a teaching to modify. The isomer is expected to be preparable by the same method and to have generally the same properties. This expectation is then deemed

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the motivation for preparing the position isomers. This circumstance has arisen many times. See: *Ex parte Englehardt*, 208 USPQ 343, 349; *In re Mehta*, 146 USPQ 284, 287; *In re Surrey*, 138 USPQ 67; *Ex Parte Ulliyot*, 103 USPQ 185; *In re Norris*, 84 USPQ 459; *Ex Parte Naito*, 168 USPQ 437, 439; *Ex parte Allais*, 152 USPQ 66; *In re Wilder*, 166 USPQ 545, 548; *Ex parte Henkel*, 130 USPQ 474; *Ex parte Biel*, 124 USPQ 109; *In re Petrzilka*, 165 USPQ 327; *In re Crownse*, 150 USPQ 554; *In re Fouche*, 169 USPQ 431; *Ex parte Ruddy*, 121 USPQ 427; *In re Wiechert*, 152 USPQ 249, *In re Shetty*, 195 USPQ 753.

For example, "Position isomerism has been used as a tool to obtain new and useful drugs" (Englehardt) and "Position isomerism is a fact of close structural similarity" (Mehta, emphasis in the original). See also MPEP 2144.09, second paragraph.

Response to arguments

Applicant's argument filed 10/26/2006 has been fully considered but it is not persuasive.

Applicant's argument is well taken, but it is not persuasive enough to overcome the obviousness rejection. Please see above for more details.

Objection

6. Claims 2-17, 20, 44, 46-58, 60, 63, 85, 87, 112-143 and 200-207 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in

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independent form including all of the limitations of the base claim and any intervening claims.

Allowable Subject Matter

7. Claims 21-41, 62, 86, 88-89, 99, 100-101, 111 and 144-199 are allowed.

Conclusion

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kahsay Habte whose telephone number is (571)-272-0667. The examiner can normally be reached on M-F (9.00- 5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Wilson can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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A handwritten signature in black ink, appearing to read 'Kahsay Habte', written over the printed name.

Kahsay Habte
Primary Examiner
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KH
November 16, 2006